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DATE: Tuesday, July 22, 2003

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DB=USPT,JPAB,EPAB,DWPI,TDBD; PLUR=YES; OP=OR			
L2	(zeta adj1 potential) same liposome$	46	L2
L1	zeta adj1 potential	2882	L1

END OF SEARCH HISTORY

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L2: Entry 4 of 46 File: USPT Jul 30, 2002

DOCUMENT-IDENTIFIER: US 6426086 B1
TITLE: pH-sensitive, serum-stable liposomes

Detailed Description Text (96):
Unilamellar liposomes (20 mM) composed of either EPC or EPC/Chol/PEG-PE (3:2:0.3 molar ratio) were prepared by the reverse-phase evaporation method (Szoka, F. C. Proc. Natl. Acad. Sci. USA 75:4194-4198 (1978)) followed by repeated extrusion through a 0.1 .mu.m pore membrane (Szoka, F. C. et al., Biochim. Biophys. Acta 601:559.mu.571 (1980)). Encapsulation of fluorescent markers into liposomes was performed by using an isotonic aqueous solution of HPTS-DPX-HEPES (35 mM-50 mM) pH 7.2. Untrapped dye was removed by gel exclusion chromatography on Sephadex G-50. Phospholipid concentrations were determined by phosphate assay (Morrison, W. R. Anal. Biochem. 7:281-284 (1964)). Liposomes were mixed with polymers and gently stirred overnight at 4.degree. C. to form liposome-polymer complexes. The mean diameter of EPC liposomes and SSL were 160.+-.40 un and 125.+-.30 nm, respectively, as determined by dynamic light scattering (Coulter N4 Particle Size Analyzer) and remained unchanged by the presence of the polymer at the polymer/lipid ratios tested. Ten microliters of the complex (corresponding to 280 .mu.g of lipid) were added to 2 mL of buffer and the release of liposome contents was monitored by fluorescence dequenching assay using liposomes with encapsulated HPTS-DPX. The extent of contents release was calculated from excitation fluorescence intensity of HPTS at .lambda..sub.ex =413 nm after a 5 min exposure to different pH at 37.degree. C. (pH-independent isosbestic point, .lambda..sub.em =512 nm (Daleke, D. L. et al., Biochim. Biophys. Acta 1024:352-366 (1990)) over that obtained after sample lysis in 0.1% (m/v) C.sub.12 E.sub.8 (100% release). Zeta potentials were derived from electrophoretic mobility measurements in 2 mM Tris-HCl, pH 8, containing 10% sucrose (m/v), using a Zetasizer 4 (Malvern Instruments, Ltd., UK) after adjustment to a negatively charged standard (AZ55, Malvern).

Detailed Description Text (101):
SSL containing specific ligands at their surface are efficiently internalized by target tumor cells whereas SSL lacking the targeting device are not (Park, J. W. et al., Proc. Natl. Acad. Sci. USA 92:1327-1331 (1995); Kirpotin, D. et al., Biochemistry 36:66-75 (1997)). Therefore, it appears attractive to confer additional pH-sensitive properties to internalizable SSL formulations for tissue-specific intracytoplasmic drug delivery in vivo. Experiments on contents release with SSL show results similar to those obtained with EPC liposomes (FIG. 2B). The presence of cholesterol, and more importantly, the incorporation of 6 mol % PEG-PE, do not seem to prevent contents release upon acidification and in the presence of poly(NIPA-co-MAA-co-ODA). This is supported by electrophoretic mobility data showing that the zeta potential of liposome-poly(NIPA-coMAA-co-ODA) complexes (polymer/lipid=0.28 m/m, 0.02 mol/mol) are about -15 mV for EPC and -6 mV for SSL-associated polymer, respectively, whereas EPC and PEGylated liposomes show a neutral particle surface. This difference in zeta potential can be explained either by shielding of the polymer charge by PEG at the surface of the complex (Woodle, M. C. et al., Biophys. J. 61:902-910 (1992)), or by reduced binding efficiency of polymer to PEG-coated liposomes.

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L2: Entry 5 of 46 File: USPT May 7, 2002

DOCUMENT-IDENTIFIER: US 6383814 B1
TITLE: Cationic amphiphiles for intracellular delivery of therapeutic molecules

Other Reference Publication (50):
Takeuchi et al., "Effect of Zeta Potential of Cationic Liposomes Containing Cationic Cholesterol Deratives on Gene Transfection," FEBS Letters, 397, pp. 207-209 (1996).

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L2: Entry 9 of 46 File: USPT Oct 16, 2001

DOCUMENT-IDENTIFIER: US 6303378 B1
TITLE: Methods for preparing polynucleotide transfection complexes

Detailed Description Text (61):
Methods for characterization of DNA/liposome complexes include spectrophotometric analysis at 400 nm, zeta potential analysis using a Brookhaven Zetaplus (Brookhaven Instruments, Holtsville, N.Y.), particle sizing using a NiComp 370, and dextrose density centrifugation (described below). In addition, in vivo transfection activity of the complexes was determined by CAT expression in the lungs of ICR mice 24 hr after a 200 .mu.IV tail vein injection. CAT expression was determined by ELISA assay and normalized to the amount of total protein (ng CAT/mg total protein).

Detailed Description Text (69):
The data in Table 1 show slight variations in OD400, size and zeta potential between the 1:6 and 1:12 complexes. Since each of these measurements are based on mean values of entire populations, however, the differences may simply be due to the presence of excess free liposome. Centrifugation profiles show similar results with the exception of the additional free liposome. Populations associated with DNA/liposome complexes appear to be the same in both formulations.

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L2: Entry 11 of 46 File: USPT Aug 7, 2001

DOCUMENT-IDENTIFIER: US 6271206 B1
TITLE: Sonic nebulized nucleic acid/cationic liposome complexes and methods for pulmonary gene delivery

Detailed Description Text (24):
CMV-CAT/DOTMA:DOPE and CMV-CAT/DOTMA:Chol complexes at a charge ratio of 1:3 (-:+) were formulated in 10% (w/v) lactose by mixing the plasmid with the liposomes under controlled conditions using a continuous infusion apparatus. The plasmid DNA concentration was 200 .mu.g/mL. The mean diameter and zeta potential of the complexes were characterized via dynamic light scattering, using a Coulter N4 MD Sub-Micron Particle Size Analyzer (Coulter Corp., Hialeah, Fla.), and via Doppler electrophoretic light scattering (Coulter DELSA 440 (Coulter Corp., Hialeah, Fla.)). Analyses were performed by collecting the scattered light from four different angles. The frequency of operation of the instrument was about 500 Hz and the amplitude of current was equal to or lower than the conductivity of the sample. The mean diameters were as shown in FIG. 2, and the zeta potential measurements showed that overall charge on the complexes was positive. The complexation efficiency was determined by agarose gel electrophoresis and found to be 100% for complexes prepared at a charge ratio (-:+) of 1:3.

Detailed Description Text (51):
CMV-CAT/DOTMA:Chol complexes (530 nm diameter, 1:3 (-:+) charge ratio) were prepared as described above. The optimized plasmid/lipid complexes with controlled colloidal and surface properties, which gave high levels of transgene expression following intratracheal instillation, were then aerosolized using an ultrasonic nebulizer. These complexes were aerosolized using an ultrasonic nebulizer to assess the stability of the plasmids and the plasmid/lipid complexes, as well as in vivo transgene expression in rat lungs following intratracheal instillation and inhalation of the aerosolized complex. The DNA remained complexed to the cationic liposomes and the integrity of the plasmid was maintained (see FIG. 8, showing that the fraction of supercoiled form of plasmid in pre- and post-nebulized samples was similar). The mean diameter of the complex before nebulization was 530.+-.329 nm. The mean diameter of the complex remaining in the nebulizer after nebulization for 10 or 20 minutes was 481.+-.289 and 510.+-.361 nm, respectively. Zeta potential measurements showed that the surface charge of the particles was unchanged after the nebulization process. These findings demonstrate that the colloidal properties of the plasmid/lipid complex were maintained after nebulization and that the binding of DNA to cationic liposomes can protect the DNA from shear induced during droplet formation.. The mass median aerodynamic diameter (MMAD) of aerosols generated using the ultrasonic nebulizers was less than 5 .mu.m, indicating that the particles are in the respirable range (see FIG. 9).

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L2: Entry 19 of 46 File: USPT Dec 28, 1999

DOCUMENT-IDENTIFIER: US 6008202 A
**** See image for Certificate of Correction ****
TITLE: Stable lipid-comprising drug delivery complexes and methods for their production

Brief Summary Text (12):
The complexes of the invention comprise a drug/lipid complex formed by mixing the drug to be delivered with cationic liposomes in a drug to lipid ratio such that the drug/lipid complex formed has a net positive charge and a drug/lipid/polycation complex formed by mixing drug with cationic liposomes and polycation in a drug to lipid to polycation ratio such that the drug/lipid/polycation complex formed has a net positive charge. By "net positive charge" as applied to the drug/lipid complex is meant a positive charge excess of lipid to drug. By "net positive charge" as applied to the drug/lipid/polycation complex is meant that the positive charges of the cationic lipid and the polycation exceed the negative charge of the drug. However, it is to be understood that the present invention also encompasses drug/lipid and drug/lipid/polycation complexes having a positively charged surface irrespective of whether the net charge of the complex is positive, neutral or even negative. A positively charged surface of a complex may be measured by the migration of the complex in an electric field by methods known to those in the art such as by measuring zeta potential (Martin, A., Swarick, J., and Cammarata, A., Physical Pharmacy & Physical Chemical Principles in the Pharmaceutical Sciences, 3rd ed. Lea and Febiger, Philadelphia, 1983), or by the binding affinity of the complex to cell surfaces. Complexes exhibiting a positively charged surface have a greater binding affinity to cell surfaces than complexes having a neutral or negatively charged surface. Furthermore, the positively charged surface could be sterically shielded by the addition of non-ionic polar compounds, of which polyethylene glycol is an example.

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L2: Entry 37 of 46 File: USPT Nov 12, 1996

DOCUMENT-IDENTIFIER: US 5573779 A
TITLE: Liposome composition

Detailed Description Text (7):
Table 2 shows the results of the measurement of the .zeta.-potentials (zeta potentials) of the liposomes thus obtained.

Detailed Description Text (13):
On the other hand, liposomes containing dicetyl phosphate which is an acidic phospholipid similar to phosphatidylinositol, had a higher negative charge (Table 2) than those containing phosphatidylinositol but effected no significant migration to Peyer's patches. These facts suggest that the high ability to migrate into Peyer's patches of the liposomes containing phosphatidylinositol as a lipid constituting the membrane have been achieved via some recognition system other than the zeta potential.